DRAWINGS

Applicants will delay filing of formal drawings until after receipt of the "Notice of Allowability" (PTO-37).

REMARKS

Claims 10-21 are pending. The Examiner has withdrawn a) the rejections of claims 10-20 under 35 U.S.C. § 112, first paragraph; b) the rejection of claims under 35 U.S.C. 102(b) as being anticipated by Imrich et al.; and c) the rejection of claims 12 and 16 under 35 U.S.C. 103(a), set forth in the previous office action. The Examiner has rejected claims 1-21 based on new rejections under 35 U.S.C. § 103.

This invention relates to one-step immunoassays for extracted analytes which permit efficient extraction of analytes from samples, while minimizing sample manipulation following extraction. The sample extractions are carried out in separately provided assay chambers which are not in fluid communication with the sample receiving region of the immunoassay device at the time of extraction, i.e., the sample extraction chamber is separate from the lateral flow immunochromatographic device. This permits greater control over mixing of the sample with the extraction reagents, and the duration of the extraction procedure, prior to immersion of the immununochromatographic device into the extracted sample. This added control over extraction conditions permits greater efficiency of extraction, and increased sensitivity of the assay. Moreover, because the extraction is performed in a separate assay chamber, these assays do not require a complex plastic or cardboard housing, a sample chamber built into a plastic housing, or specially designed swabs to fit in the

complex housings to help control flow of the sample from a built-in sample chamber to the sample receiving region of the immunoassay test strip.

These features permit the assays of the subject invention to be performed by individuals without extensive training in laboratory techniques, and provide greater sensitivity as a result of added control over extraction conditions.

Rejections Under 35 U.S.C. § 103

Claims 10-11, 13-15 and 17-21 have been rejected under 35 U.S.C. § 103 as obvious over Imrich et al., in view of Hochstrasser (U.S. Patent 4,059,407). Claims 12 and 16 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Imrich et al. and Hochstrasser, in view of Bogart et al. (U.S. Patent No. 5,494, 801) and Murray (U.S. patent No. 3,957,436).

Applicants respectfully disagree that any of the claims are obvious over Imrich in view of Hochstrasser.

Imrich teaches the use of certain devices containing immunodiagnostic test strips housed in plastic casings for the detection of certain analytes, The Examiner accurately notes, however, that "Imrich does not teach dipping the device into another chamber." Office Action mailed 12/19/01 at page 5, ¶ 5. In fact, the devices in Imrich are described as containing a built-in extraction chamber in flow communication with the immunoassay test strip matrix--thereby eliminating the need for a separately provided extraction chamber:

> The devices generally comprise an extraction chamber, a labelling zone having a means for specifically labelling the analyte; and a matrix defining an axial flow path in fluid communication with the extraction chamber, which matrix comprises a sample receiving zone and capture zone located downstream from the sample receiving zone. (Imrich, col. 2, lines 26-32).

See also Imrich at col. 4, lines 24-26 ("The extraction chamber is fluidly connected to the matrix by means of an exit port located distally in the chamber."). See also Imrich, at Col. 7, ll. 30-41 (describing construction of the device having a plastic casing containing the sample processing region and the test strip).

The methods described in Imrich therefore do not include the step of providing an assay chamber which is physically separate from the lateral flow device. Thus, because the extraction chamber is built into the same plastic casing as the immunodiagnostic matrix, Imrich fails to describe inserting the device into a separate sample chamber.

Moreover, the sample chamber and test strip are combined into one plastic casing for ease of use: "Conveniently, the matrix is contained within a solid casing. The extraction chamber is formed as an integral part of the top of the solid casing." Imrich, col. 7, ll. 11-13.

Although Imrich describes the placement of filters in the extraction chamber between the sample and the exit port, it discusses only that the filters may be used to slow the exit of fluid from the extraction chamber before flowing onto the matrix of the test strip. Imrich, however, does not state that the filters may be used to stop the flow of extracted sample onto the matrix of the test strip:

> Filters may be placed in the extraction chamber between the sample and the exit port. The filters may act to remove particulate matter from the sample to improve flow kinetics on the matrix. The filters may also slow the egress of fluid from the extraction chamber to the matrix. This may prolong the treatment time of the analyte prior to the assay to maximize analyte availability.

Imrich at col. 7, ll. 42-49.

In contrast to the methods described in Imrich, the methods claimed in Claims 10-21 of the instant application are directed to methods in which an assay chamber separate from the immunoassay device is provided in which to perform the sample extraction. Moreover, in the methods of claims 10-21, the immunoassay device is inserted into the assay chamber to contact the extracted sample after sample extraction, and is not in fluid communication with the assay chamber prior to insertion into the assay chamber.

The Examiner indicates that although Imrich contains no description of immersing its immunodiagnostic device into an extracted sample, Hochstrasser describes immersing certain indicator instruments for measurement of chemical substances, into a sample.[1] The Examiner therefore asserts that the claimed invention would be obvious in view of Imrich and Hochstrasser.

Applicants respectfully disagree. Imrich describes only the use of devices containing both the immunoassay test strip and an extraction chamber fluidly connected with the test strip. Imrich does not explicitly describe or suggest a method for detecting a Strep A antigen where the assay chamber is separately provided from the immunoassay device and the immunoassay test strip is immersed into the extracted sample to initiate sample flow through the test strip. Additionally, Hochstrasser does not teach the construction or use of an immunodiagnostic test strip for use in detecting a Strep A antigen, or the immersion of such a test strip into an extracted sample.

Moreover, the Examiner has not cited any specific teaching to combine the two references:

> Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence." [citations omitted].
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> Nowhere does the Board particularly identify any suggestion, teaching, or motivation to combine the children's art references (Holiday and Shapiro) with the conventional trash or lawn bag references, nor does the Board make specific--or even inferential--findings concerning the identification of the relevant art, the level of ordinary skill in the art, the nature of the problem to be solved, or any other factual findings that might serve to support a proper obviousness analysis. See, e.g., Pro-Mold & Tool, 75 F.3d at 1573, 37 USPQ2d at 1630.
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> To the contrary, the obviousness analysis in the Board's decision is limited to a discussion of the ways that the multiple prior art references can be combined to read on the claimed invention. . . . Yet this reference-by-reference, limitation-by-limitation analysis fails to demonstrate how the Holiday and Shapiro references teach or suggest their combination with the conventional trash or lawn bags to yield the claimed invention. [citation omitted]. Because we do not discern any finding by the Board that there was a suggestion, teaching, or motivation to combine the prior art references cited against the pending claims, the Board's conclusion of obviousness, as a matter of law, cannot stand. See C.R. Bard, 157 F.3d at 1352, 48 USPQ2d at 1232; Rouffet, 149 F.3d at 1359, 47 USPQ2d at 1459; Fritch, 972 F.2d at 1265, 23 USPQ2d at 1783; Fine, 837 F.2d at 1075, 5 USPQ2d at 1600; Ashland Oil, 776 F.2d at 297, 227 USPQ at 667.

In Re Dembiczak, 50 U.S.P.Q.2d 1614, 1617-18 (Fed. Cir. 1999) (emphasis added).

Thus, to establish the obviousness of the claimed invention, more is needed than to identify different elements in multiple references, or to use the claimed invention to reconstruct how the references might be used to obtain the claimed invention. In fact, Imrich teaches against the use of separate extraction chambers, because separate extraction of samples require the user to "return later to transfer the acid solution to the assay medium. Multi-step assays such as these require more time and attention from

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[1] Note also that the indicator instrument of Hochstrasser differs in many features from the test strips of the instant invention.

health care personnel and thus are more expensive than one step assays." Imrich *et al.* at col. 1, lines 61-66. Imrich further teaches away from use of a separate extraction chamber, because it has placed the test strip matrix and the sample extraction chamber into the plastic casing for ease of use.

The Federal Circuit has recently reiterated the requirement that there be a specific showing of a specific suggestion, teaching, or motivation to combine prior art references:

> "The factual inquiry whether to combine references must be thorough and searching . . . See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an `essential component of an obviousness holding'") (quoting C.R. Bard, Inc., v. M3 Systems, Inc., 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232(Fed. Cir. 1998)); In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617(Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637(Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600(Fed. Cir. 1988) ("`teachings of references can be combined only if there is some suggestion or incentive to do so.'") (emphasis in original) (quoting ACS Hosp. Sys., Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577, 221 USPQ 929, 933(Fed. Cir. 1984)).
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> The need for specificity pervades this authority. See, e.g., In re Kotzab, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317(Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed"); In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459(Fed. Cir. 1998) ("even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination.
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> In other words, the Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."); In re Fritch, 972

F.2d 1260, 1265, 23 USPQ2d 1780, 1783(Fed. Cir. 1992) (the examiner can satisfy the burden of showing obviousness of the combination "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references").

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The examiner's conclusory statements that "the demonstration mode is just a programmable feature which can be used in many different device[s] for providing automatic introduction by adding the proper programming software" and that "another motivation would be that the automatic demonstration mode is user friendly and it functions as a tutorial" do not adequately address the issue of motivation to combine. This factual question of motivation is material to patentability, and could not be resolved on subjective belief and unknown authority. It is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to "[use] that which the inventor taught against its teacher." W.L. Gore v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

In Re Lee, 61 U.S.P.Q.2d (BNA) 1430, 1433-34 (Fed. Cir. 2002) (emphasis added).

Applicants respectfully assert that there is no specific motive to combine the method for the immersion of the instruments in Hochstrasser with use of the devices in Imrich et al. to obtain the methods of the claimed invention.

Because the immunoassay devices in Imrich contain both the sample extraction chamber and the test strip, Imrich does not state or suggest that the device can be inserted into a separate sample chamber while operating the device. In fact, such a suggestion would offset any convenience provided by Imrich's placement of the sample extraction chamber and the test strip in one plastic casing. Indeed, to combine Imrich with Hochstrasser's "sample immersion method," it would be necessary to use two of the Imrich devices to carry out such a method. That is, one Imrich device containing a test strip would have to be immersed into the sample extraction chamber of a second

Imrich device. In addition, during the immersion, the sample in the sample chamber of the first device would begin flowing from the chamber onto the test strip within the first device, making length of contact of the test strip in the second device dependent on the rate of outflow from the sample chamber in the first device. Moreover, the bulk of the plastic casing of the Imrich device would make such immersion difficult if not impossible. Therefore, such a method would be inconsistent with any convenience afforded by combining the sample chamber and test strip into one plastic housing, and with avoiding the need to return after sample extraction to take further steps to perform the assay.

Consequently, Imrich fails to teach, and teaches away from, immersing the test strip into a separate sample chamber following sample extraction. Thus, one of ordinary skill in the art would not have been motivated to combine Imrich with Hochstrasser to obtain the methods of the claimed invention.

The commercial success of a device embodying claimed features of the invention further supports the non-obviousness of the claims. In the claimed device, spatial separation of the separate assay chamber and lack of fluid communication between the assay chamber and the separate lateral flow immunochromatographic assay test strip permits greater control over the length and efficiency of extraction, and the sensitivity of the assay. For example, as noted at page 63 of the specification, a device within the scope of the claimed invention is able to detect Streptococcus cells when present at a concentration as low as 4×10^5 per swab, while the one-step Quidel device can detect Streptococcus cells only when present at a concentration of 8×10^5 cells/swab. In addition, in a study comparing the sensitivity of the OSOM™ Strep A test with the sensitivity of the Quidel QuickVue™ Strep A test, Dr. Richard H. Schwartz determined

that the OSOM™ Strep A test had an overall sensitivity of 95%, while the QuickVue™ Strep A test had an overall sensitivity of 87%. Declaration of Richard H. Schwartz at ¶ 3; Schwartz submitted with preliminary amendment, Richard H., Pediatric Infectious Disease J., 16(11):1099-1100 (November 1997), Exhibit 2 to the Declaration of Richard H. Schwartz. The commercial success of the OSOM™ Strep A test also establishes that claim 21, specifying that the assay detects as low as 4 X 10^5 cells/sample, is not obvious in view of Imrich.

The increase in sensitivity observed with the OSOM™ Strep A test is the direct result of providing a separate assay chamber and then inserting the the immunochromatographic device into the assay chamber to initiate lateral flow through the immunochromatographic device, rather than having the extraction chamber in flow communication with the sample receiving region of the immunoassay test strip. Thus, the commercial success of the OSOM product is directly related to the claimed features of the invention which require "providing an assay chamber which his separate from the lateral flow immunochromatographic device," and the need for "inserting said sample receiving region of said lateral flow immunochromatographic device into said assay chamber and contacting said liquid extract" thereby permitting more efficient extraction. (See Declaration of Richard H. Schwartz at ¶ 4). A finding of non-obviousness is proper where there is evidence of commercial success of a product, having as a critical feature the claimed invention. Perkin-Elmer Corp. v. ComputerVision Corp., 732 F.2d 888, 221 USPQ 669 (Fed. Cir.), cert. denied, 469 U.S. 857)1994. Thus, claims 10-11, 13-15, and 17-21 are not made obvious by Imrich in view of Hochstrasser.

Claims 12 and 16 are likewise not obvious when Imrich, Hochstrasser, Bogart, and Murray (US 3,957,436) are taken together because they do not teach a method for determining the presence or absence of a Streptococcus antigen, where separate immunoassay devices and an extraction chamber are provided, where the extraction solution comprises 0.2-5M sodium nitrite and 0.02-2M acetic acid, or where the solution contains a color indicator to indicate proper preparation. As discussed above, Imrich fails to teach, and teaches against the use of a method for the detection of an analyte where the immunoassay test strip is inserted into a separately provided extraction chamber.

In addition, as previously noted at page 10 of the Office action mailed 9/2/98, Imrich does not teach vigorous mixing of the swab and extraction reagents for at least 10 seconds, or an extraction solution where the addition of 0.3 M acetic acid to a color-indicator spiked 2 M sodium nitrite solution changes the color of the final extraction solution.

Applicants therefore respectfully assert that neither claims 12 and 16, nor claims 10-11, 13-15 or 17-21 are obvious in light of Imrich et al. and Hochstrasser, either together or in combination with Bogart and/or Murray.

CONCLUSION

For the reasons set forth above, Applicants respectfully assert that claims 10-21 are not made obvious by Imrich et al., which describes only methods using devices in which the immunoassay test strip is in flow communication with the extraction chamber. Claims 10-21 are directed to methods for detecting a Streptococcus antigen where an immunoassay device, and a separate assay chamber are provided, and where the immunoassay device is inserted into the assay chamber after completion of extraction of the sample. There is no motivation to combine Imrich with Hochstrasser, and, thus, those references cannot render the claimed invention obvious . Applicants thus believe that the claims are in condition for allowance.

Respectfully submitted,

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